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09/364,847 07/30/99 PEOPLES

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EXAMINER

STEADMAN, D

ART UNIT

PAPER NUMBER

1652

DATE MAILED:

12/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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# Office Action Summary

Application No.

09/364,847

Applicant(s)

PEOPLES ET AL.

Examiner

David J. Steadman

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☒ Claim(s) 2 is/are objected to.
- 8) ☐ Claims \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☒ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

## Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

## **DETAILED ACTION**

### ***Status of the Application***

Claims 1-6 are pending.

The amendment of claims 1 and 2, reiteration of claims 3-6 and cancellation of claims 7-14 is acknowledged.

Receipt of the information disclosure statement filed 01/11/00 (paper number 5) and the supplementary information disclosure statement filed 03/06/00 (paper number 6) is acknowledged. The supplementary information disclosure statement filed 03/06/00 (paper number 6) has been filed with the application and has been considered. However, due to the relatively large list of references included with the information disclosure statement filed 01/11/00 (paper number 5), the references were not filed along with the application. Examiner's attempt to locate these references for consideration during examination of the instant application was unsuccessful. It is suggested that additional copies of the references listed in the information disclosure statement filed 01/11/00 (paper number 5) be submitted for consideration by the examiner. If additional copies of references are submitted, please send to the attention of David J. Steadman. The examiner will consider the references listed in the information disclosure statement filed 01/11/00 (paper number 5) upon receipt.

### ***Oath/Declaration***

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Art Unit: 1652

The oath or declaration is defective because:

The country of citizenship of Oliver Peoples is listed as Scottla. This appears to be a truncated and, possibly misspelled, version of Scotland.

### ***Claim Objections***

2. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 2 fails to further limit the  $\beta$ -ketothiolase-acetoacetyl-CoA reductase fusion enzyme of claim 1.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a  $\beta$ -ketothiolase-acetoacetyl-CoA reductase fusion enzyme. As written, the claim reads on a product of nature and should be amended to indicate the hand of the inventor, for example, by insertion of "purified". See MPEP § 2105.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1652

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "PHA" in claim 1 (claims 2-6 dependent thereon) is a relative term which renders the claim indefinite. The term "PHA" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the term "PHA" be replaced with, for example, "polyhydroxyalkanoate".

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-3 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bulow et al. (Trends Biotech 9:226-231, 1991) in view of Peoples et al. (J Biol Chem 262:97-102, 1987) and Peoples et al. (Mol Microbiol 3:349-357, 1989). Claims 1-3 are drawn to a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker between zero and 50 amino acids. Claim 6 is drawn to expression of a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a bacteria.

Bulow et al. teach fusion enzymes expressed in *Escherichia coli* that catalyze sequential catalytic steps, namely a  $\beta$ -galactosidase-galactokinase protein fusion that catalyzes 1) the hydrolysis of lactose to glucose and galactose, followed by 2) phosphorylation to galactose-1-phosphate (page 228, Fig. 3). Bulow teach that “When corrected for the increase in molecular weight caused by the fusion, the specific activities correspond to 50-100% of those for the native enzymes” (page 230, column 1). “Furthermore, only modest changes in  $K_m$ , pH-optima, thermostability... have been observed” (page 230, column 1). Bulow et al. also teach advantages of fusion enzymes that catalyze sequential steps, such as facilitated purification, favorable enzyme kinetics, and proximity effects whereby an intermediate product can be transferred efficiently to the desired second enzyme, instead of a competing enzyme (page 226). Bulow et al. further teach that “fairly short linkers (two to ten amino acid residues) are optimal – longer linkers are often prone to proteolytic degradation in vivo and the final yield of recombinant enzymes can be reduced severely” (page 230, column 1). Bulow et al. also teach that “the order of the genes, which determines which enzyme forms the N-terminus of the final gene product, is chosen arbitrarily” and that “the reason this design principle can, in general be applied successfully is that the N- and C-termini of the proteins are charged and therefore usually located on the surface. The native tertiary structure of the constituent proteins thus remains almost intact in the recombinant enzyme” (page 227, column 1). Bulow et al. do not explicitly teach a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme or expression of such a fusion enzyme in a bacteria.

Peoples et al. (1987) teach the cloning, nucleotide and amino acid sequences and *E. coli* expression of *Zoogloea ramigera*  $\beta$ -ketothiolase.

Peoples et al. (1989) teach the cloning, nucleotide and amino acid sequences and expression of *Zoogloea ramigera* acetoacetyl coenzyme A reductase in *E. coli*.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Bulow et al., Peoples et al. (1987) and Peoples et al. (1989) for a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker between zero and 50 amino acids. Also, bacterial expression systems are well known in the art and one of ordinary skill would have recognized that a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme can be expressed in a bacteria at the time of the invention. One would have been motivated to generate a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker between zero and 50 amino acids and express the fusion enzyme in bacteria because of the teachings of Bulow et al. as described above. One would have a reasonable expectation of success for generating a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker between zero and 50 amino acids and expressing said fusion enzyme in a bacteria because of the results of Bulow et al., Peoples et al. (1987) and Peoples et al. (1989). Therefore, claims 1-3, drawn to a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker between zero and 50 amino acids and claim 6, drawn to expression of a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a bacteria would have been obvious to one of ordinary skill in the art.

5. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bulow et al. in view of Peoples et al. (1987) and Peoples et al. (1989) as applied to claims 1-3 and 6 above and further in view of Argos (J Mol Biol 211:943-958, 1990). Claim 4 is drawn to a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a glycine-serine linker.

Bulow et al, Peoples et al. (1987) and Peoples et al. (1989) disclose the teachings as described above. The combined teachings of Bulow et al, Peoples et al. (1987) and Peoples et al. (1989) do not explicitly teach using a glycine-serine linker.

Argos teaches advantages of using a glycine-serine oligopeptide linker. Such advantages include flexibility of the linker provided by glycine due to its relatively small side chain, conformational and energetic stability due to hydrogen bonding of the polar side chain of serine with solvent in an aqueous environment and reduced susceptibility to of a glycine-serine oligopeptide linker to proteolysis (page 947).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Bulow et al., Peoples et al. (1987), Peoples et al. (1989) and Argos for a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker consisting of glycine-serine residues. One would have been motivated to generate a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker consisting of glycine-serine residues because of the teachings of Bulow et al. and Argos as described above. One would have a reasonable expectation of success for generating a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a linker consisting of glycine-serine residues because of the results of Bulow et al, Peoples et al. (1987), Peoples et al. (1989) and Argos. Therefore, claim 4, drawn to a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme with a consisting of glycine-serine residues would have been obvious to one of ordinary skill in the art.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bulow et al. in view of Peoples et al. (1987) and Peoples et al. (1989) as applied to claims 1-3 and 6 above and



further in view of Somerville et al. (US Patent 5,610,041, 1997). Claim 5 is drawn to expression of a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a plant.

Bulow et al, Peoples et al. (1987) and Peoples et al. (1989) disclose the teachings as described above. The combined teachings of Bulow et al, Peoples et al. (1987) and Peoples et al. (1989) do not explicitly teach expression of a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a plant.

Somerville et al. teach expression of  $\beta$ -ketothiolase and acetoacetyl CoA reductase in *Arabidopsis thaliana*. Somerville et al. disclose that expression of such heterologous proteins is applicable to any higher plant for which a method of transformation is available. Somerville et al. also provide an advantage of producing PHA/PHB in genetically engineered plants expressing  $\beta$ -ketothiolase and acetoacetyl CoA reductase, namely, reduced cost of production. Somerville et al. do not explicitly teach expression of a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in *A. thaliana*.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Bulow et al., Peoples et al. (1987), Peoples et al. (1989) and Somerville et al. for a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme expressed in a plant. One would have been motivated to express a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a plant because of the teachings of Bulow et al. and Somerville et al. as described above. One would have a reasonable expectation of success for expressing a  $\beta$ -ketothiolase-acetoacetyl CoA reductase fusion enzyme in a plant because of the results of Bulow et al, Peoples et al. (1987), Peoples et al. (1989) and Somerville et al. Therefore, claim 5, drawn to expression of a  $\beta$ -

Art Unit: 1652


ketothiolase-acetoacetyl CoA reductase fusion enzyme in a plant would have been obvious to one of ordinary skill in the art.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

December 27, 2000

  
NASHAAT T. NASHED PHD.  
PRIMARY EXAMINER